in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a PI 3-kinase inhibitor or a pharmaceutically acceptable salt thereof, wherein at least a portion of the resident macrophages in the central nervous system of the subject comprise one or more PI 3-kinase mutations. In some embodiments, at least a portion of the resident macrophages in the central nervous system of the subject are $PIK3CA^{H1047R+}$. In some embodiments, the PI 3-kinase inhibitor is selected from the group consisting of idelalisib, BKM120, GDC-0980, PF-04691502, XL147, IPI-145, BYL719, SF1126, BAY80-6946, GSK2126458, NVP-BEZ235, GDC-0941, PX-866, XL765, and ZSTK474.

[0015] In some embodiments of the methods disclosed herein, the route of administration of the PI 3-kinase inhibitor is parenteral, intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, oral, sublingual, intranasal, intracerebral, intrathecal, intravaginal, transdermal, rectal, by inhalation, or topical.

[0016] In another aspect, the present disclosure relates to non-human animals, for example rodents, that conditionally express a mutant BRAF allele that confers a pathological phenotype on the non-human animal expressing the allele. In one embodiment, the pathological phenotype is histiocytosis.

[0017] In one embodiment, the non-human animal of the disclosure is characterized by expression of $BRAF^{V600E}$ in erythromyeloid progenitors.

[0018] In another aspect, the non-human animals comprise a mutant BRAF allele flanked upstream and downstream with site-specific recombinase recognition sites (SRRSs), and the non-human animal comprises a recombinase that recognizes the SRRSs, wherein the recombinase is inducible.

[0019] In a another aspect, the present disclosure relates to a genetically modified mouse that comprises a nucleic acid construct comprising a mutant exon encoding a $BRAF^{V600E}$ mutation, wherein the mutant is flanked upstream and downstream by SRRSs and the mouse comprises an inducible recombinase gene encoding a recombinase. In one embodiment, the SRRSs are recognized by the inducible Cre recombinase.

[0020] In one aspect, the present disclosure relates to a genetically modified mouse comprising the genotype $Csf1r^{iCre}$; $BRAF^{V600E}$; $Rosa26^{LSL\text{-}YFP}$.

[0021] In another aspect, the present disclosure relates to a method for recapitulating development of neurodegeneration in clonal histiocytic disorders comprising: (a) providing a transgenic mouse whose genome comprises a $BRAF^{V600E}$ transgene and a $Rosa26^{LSL\text{-}YFP}$ transgene, the transgenes operably linked to a tamoxifen-inducible regulatory sequence for expression of $BRAF^{V600E}$ and YFP in erythromyeloid progenitors (EMPs) of said mouse, and $Csf1r^{MeriCreMer}$; (b) contacting said mouse in utero with 4-hydroxy-tamoxifen (OH-TAM) wherein expression of $BRAF^{V600E}$ and $Rosa26^{LSL\text{-}YFP}$ is induced in EMPs of said mouse. The mouse (embryo) is exposed to OH-TAM at E8.5.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] FIG. **1** is a schematic showing that the erythromyeloid progenitors (EMP) from the yolk sac colonize the fetal liver and give rise to macrophage (MΦ) precursors that colonize the embryo from E9.5 in a Cx3cr1-dependent manner, to give rise to adult F4/80+ resident macrophages. MΦ specification, starting from E10.25, is initiated by the expression of tissue-specific transcriptional regulators.

[0023] FIG. **2** is a schematic showing the developmental diversity of the myeloid system. EMPs emerge in the yolk sac at E8.5, migrate to the fetal liver, and give rise to fetal macrophages in vivo. Resident macrophages develop from EMPs in the absence of Myb and persist as residents in post-natal tissues. Within the embryo proper, the hemogenic endothelium of large arteries gives rise to Hematopoietic Stem Cells (HSCs) at ~E10.5. HSCs migrate to the fetal liver and to the bone marrow, where they persist, self-renew throughout life, and give rise to adult-type red blood cells, lymphoid cells and short-lived myeloid cells.

[0024] FIGS. **3**A-**3**D show constitutive expression of $BRAF^{V600E}$ in Csf1r+ cells. (FIG. **3**A) is a graphic showing the breeding scheme. (FIG. **3**B) Embryonic lethality of $Csf1r^{iCre+}$; $BRAF^{V600E}$. $Rosa26^{LSL\text{-}YFP}$ mice, black bars represent the % of mice born from the cross depicted in (FIG. **3**A) according to their genotype (n=39). (FIG. **3**C) Brightlight (upper panel) and epifluorescence microscopy (lower panel) of $Csf1r^{iCre+}$; $BRAF^{WT}$; $Rosa26^{LSL\text{-}YFP}$ and $Csf1r^{iCre+}$; $BRAF^{V600E}$; $Rosa26^{LSL\text{-}YFP}$ embryos showing hemorrhagic foci in the liver (arrow) and accumulation of YFP+ cells in fetal liver. Cross (t) indicates dead embryo. (FIG. **3**D) $Csf1r^{iCre+}$; $BRAF^{V600E}$; $Rosa26^{LSL\text{-}YFP}$ mice are associated with 100% lethality beyond E14.5.

[0025] FIG. **4** shows Tamoxifen-inducible mouse models used to target EMP versus HSC. $Csf1^{MeriCreMer}$; $Rosa26^{LSL\text{-}YFP}$ do not target HSCs in adult mice, while pulse-labeling of $Cxcr4^{CreERT2+}$; $Rosa26^{LSL\text{-}YFP}$ results in labeling of 10% HSCs. LSK: Lin-Sca1+Kit+.

[0026] FIGS. **5**A-**5**E show the results of experiments with a $Csf1r^{MeriCreMer}$; $BRAF^{V600E}$; $Rosa26^{LSL\text{-}YFP}$ inducible model. (FIG. **5**A) Breeding scheme. (FIG. **5**B) % of mice born from the cross depicted in (FIG. **5**A) according to their genotype (n=201). (FIGS. **5**C and **5**D) Flow cytometric analysis and IF analysis of livers of 4-week old mice. YFP+ cells are F4/80hi CD11blo (gated on CD45+ cells). (FIG. **5**E) Histologic analysis of the brain. Clusters of YFP+ cells in the cerebellum and brainstem. YFP+ cells also stain for CD68 (and Iba1, not shown).

[0027] FIGS. **6**A-**6**D show neurological disease in the $Csf1r^{MeriCreMer}$; $BRAF^{V600E}$; $Rosa26^{LSL\text{-}YFP}$ model. (FIG. **6**A) Test of limb-clasping reflexes of 6-8-month old mice. When lifted by the tail $BRAF^{WT}$ mice behave normally, extending their hind limbs. In contrast, $BRAF^{V600E}$ mice bend their legs towards their trunk. (FIG. **6**B) Cumulative incidence rate of behavioral abnormalities. (FIG. **6**C) Footprint assay assessing locomotion defects. Front paws were painted with red ink, hind paws with blue ink. $BRAF^{V600E}$ mice lose coordination; front/hind legs do not overlap, and later mice are paralyzed (far right panel). (FIG. **6**D) Measurement of footprint assay. Numbers below graphs correspond to the measurements performed as displayed in (FIG. **6**C).

[0028] FIGS. **7**A and **7**B show histological analysis of the spinal cord in Cre+ $BRAF^{V600E}$ and littermate controls. (FIG. **7**A) Iba1+ microglia accumulate in the white matter. (FIG. **7**B) Flow cytometry analysis of F4/80+ macrophages from the spinal cord. Littermates are color-coded.

[0029] FIGS. **8**A and **8**B show demyelination of the spinal cord of Cre+ $BRAF^{V600E}$ mice compared to wild type mice. (FIG. **8**A) Luxol fast blue stain shows demyelination and leukocyte infiltration in the white matter of the spinal cord.